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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,201	04/07/2006	Bjarne Due Larsen	50412/015002	5189
21559	7590	01/27/2009	EXAMINER	
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			AUDET, MAURY A	
			ART UNIT	PAPER NUMBER
			1654	
			NOTIFICATION DATE	DELIVERY MODE
			01/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No. 10/534,201	Applicant(s) LARSEN ET AL.	
	Examiner MAURY AUDET	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,56-80 and 85-89 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 85-89 is/are allowed.
- 6) ☒ Claim(s) 1 and 56-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The present application has been transferred from former Examiner Young to the present Examiner.

Applicant's amendment and response is acknowledged, and the search has been extended to the species beyond the originally elected, and allowed species (now Independent Claim 89). Due to the recitation of new art of record, the application is sent Non-Final.

Election/Restrictions

As noted previously, Applicant's election without traverse of Compound 22, (H-D-Lys(4-nitrobenzoyl-Gly-OH), as the invention, in the reply filed on 10/15/07 is acknowledged. All the claims have been examined, but only as drawn to the elected compound (*speices*) of the invention, Compound 22, (H-D-Lys(4-nitrobenzoyl-Gly-OH).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 56-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al. (US 6,395,532 B1).

Jones et al. teach Gly-Lys dipeptides, bearing small or large hydrophobic side chains (see e.g. columns 16 and 19; entire document):

Acyl donors Z-L-Phe-OBn, Z-L-Ala-OBn, Z-L-Glu-OMe, and Z-L-Lys-SBn (1-4) and acyl acceptors Gly-NH.sub.2 and L-Ala-NH.sub.2 (5, 6) were used for the coupling reaction as shown in FIG. 5. The acyl donors Z-L-Phe-OBn, Z-L-Ala-OBn, Z-L-Glu-OMe, and Z-L-Lys-SBn (1-4) **provided representative examples of large and small hydrophobic, negatively charged and positively charged P.sub.1 side chains**, respectively and allowed a broad evaluation of the affinity of the S.sub.1 pocket of these enzymes for various amino acids. The small amino acid amides Gly-NH.sub.2 and L-Ala-NH.sub.2 (5, 6) were chosen as the acyl acceptors since the S.sub.1 ' pocket of subtilisins is narrow (Moree et al., J. Am. Chem. Soc., 119:3942-3947 (1997); Betzel et al., J. Mol. Biol., 223:427-445 (1992); Sears et al., J. Am. Chem. Soc., 116:6521-6530 (1994); and Jackson et al., Science, 266:243-247 (1994), which are hereby incorporated by reference), and, therefore, it accepts .alpha.-branched amino acids only poorly. The narrow nature of the S.sub.1 ' pocket is attributed to the bulky side chain of M222, this residue being a conserved residue amongst subtilisins. Siezen et al., Protein Eng., 4:719-737 (1991), which is hereby incorporated by reference. This has limited their use in peptide ligation applications.

For accurate comparison, the D-isomers Z-D-Phe-OBn, Z-D-Ala-OBn, Z-D-Glu-OMe, Z-D-Lys-OBn, and Ac-D-Phe-OBn (15-19) of the representative L-amino acids Z-L-Phe-OBn, Z-L-Ala-OBn, Z-L-Glu-OMe, and Z-L-Lys-SBn (1-4) examined in the previous ligation examples were used. The stereoselectivity of SBL-WT for L-amino acids was clear (Table 4), because none of the D-amino acid esters evaluated gave dipeptide products with WT as the catalyst. All of the S166C-MEs yielded dipeptide products containing D-amino acids Z-D-Phe-Gly-NH.sub.2, Z-D-Ala-Gly-NH.sub.2, Z-D-Glu-Gly-NH.sub.2, **Z-D-Lys-Gly-NH.sub.2**, and Ac-D-Phe-Gly-NH.sub.2 (20-24). While each of these enzymes still showed a preference for L-amino acids, yields of up to 66% of Z-D-Phe-Gly-NH.sub.2, using S166C--SCH.sub.2 C.sub.6 H.sub.5, over 0% for WT, demonstrated a dramatic improvement in SBL's acceptance of D-amino acids.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize Gly-Lys dipeptides, bearing any type of known side chain modifications well known in the peptide arts, in Jones et al., because Jones et al. advantageously teaches that small and large hydrophobic side chain modifications may be carried out on Gly-Lys dipeptides. Absent evidence to the contrary of some unexpected result (e.g. in treating arrhythmias), using one side chain alternative versus others.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Allowable Subject Matter

Claims 85-89 are in condition for allowance.

New claim 89, having now been amended commensurate in scope with the elected invention, were not found to have been reasonable taught or suggested by the prior art of record, as drawn to the originally elected species of Compound 22 of the invention, (H-D-Lys(4-nitrobenzoyl-Gly-OH).

Claims 85-88, drawn to methods of using the Gly-Lys modified conjugates of the genus of claim 1 to treat arrhythmia's were not found to be reasonably taught or suggested by the prior art of record.

Appropriate correction is required.

Conclusion

Claims 85-89 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 1/19/2008

/Maury Audet/
Examiner, Art Unit 1654